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Pre-Hospital Intravenous Fluid is Associated with Increased Survival in Trauma Patients

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Abstract

Background—Delivery of intravenous crystalloid fluids (IVF) remains a tradition-based priority during pre-hospital resuscitation of trauma patients. Hypotensive and targeted resuscitation algorithms have been shown to improve patient outcomes. We hypothesized that receiving any pre-hospital IVF is associated with increased survival in trauma patients compared to receiving no pre-hospital IVF.

Methods—Prospective data from ten Level 1 trauma centers were collected. Patient demographics, pre-hospital IVF volume, pre-hospital and Emergency Department vital signs, life-saving interventions, laboratory values, outcomes and complications were collected and analyzed. Patients who did or did not receive pre-hospital IVF were compared. Tests for non-parametric data were utilized to assess significant differences between groups ($p = 0.05$). Cox regression analyses were performed to determine the independent influence of IVF on outcome and complications.

Results—The study population consisted of 1245 trauma patients; 45 were removed due to incomplete data; 84% ($n=1009$) received pre-hospital IVF, and 16% ($n=191$) did not. There was no difference between the groups with respect to gender, age, and Injury Severity Score. The on-scene systolic blood pressure (SBP) was lower in the IVF group (110 vs. 100 mmHg, $p<0.04$) and did not change significantly after IVF, measured at ED admission (110 vs. 105 mmHg, $p=0.05$). Hematocrit/hemoglobin, fibrinogen, and platelets were lower ($p<0.05$), and Prothrombin Time/International Normalized Ratio and Partial Thromboplastin Time were higher ($p<0.001$) in the IVF group. The IVF group received a median fluid volume of 700ml (IQR: 300-1300). The Cox regression revealed that pre-hospital fluid administration was associated with increased survival, Hazard Ratio: 0.84 (95% Confidence Interval: 0.72, 0.98; $p=0.03$). Site differences in ISS and fluid volumes were demonstrated ($p<0.001$).

Conclusions—Pre-hospital IVF volumes commonly used by PROMMTT investigators do not result in increased SBP but are associated with decreased in-hospital mortality in trauma patients compared to patients who did not receive pre-hospital IVF.

Level of Evidence—II, Prospective

Keywords

pre-hospital; resuscitation; clinical parameters; PROMMTT

Introduction

Pre-hospital resuscitation with intravenous fluids (IVF) is a common practice among first responders. Fluid administration has been associated with poor outcomes including coagulopathy, organ failure, prolonged hospitalization and death^{1,2}. This tradition-based priority during resuscitation of trauma patients has not been standardized; the choice of IVF, amount and duration, is institutionally driven. PreHospital Trauma Life Support (PHTLS) has recommended an initial administration of 1 – 2 liters of crystalloid.³ If a physiologic response is not achieved, this is followed by transfusion of packed red blood cells.

Aggressive resuscitation protocols have been associated with complications related to the extravasated fluid such as abdominal compartment syndrome (ACS), acute respiratory distress syndrome (ARDS) and renal failure. Alternative solutions such as hypertonic

saline⁴⁻⁶, various starch solutions, and polymerized hemoglobins⁷ have not been shown to be superior to crystalloid for the initial resuscitation of hemorrhagic shock. These resuscitation methods have also introduced concerns for increased intravascular volumes raising blood pressure, diluting coagulation factors, and disrupting pre-formed clots⁸.

Alternatively, previous work has demonstrated that restrictive fluid algorithms in association with damage control laparotomies⁹, pre-operative optimization in torso trauma², and maintenance of a low intraoperative mean arterial pressure¹⁰ results in improved outcomes. A recent study demonstrated that damage control resuscitation defined as maintenance of systolic blood pressure (SBP) of 90 mmHg with a limited amount of IV crystalloids and high fresh frozen plasma (FFP) to packed red blood cell (PRBC) ratios, is associated with increased survival and shorter Intensive Care Unit (ICU) and hospital stays¹¹. Finally, hypotensive strategies have been noted to attenuate transfusion requirements and post-operative coagulopathy.¹²

During World War II, Lieutenant Colonel Henry Beecher advocated maintenance of an 85 mmHg SBP while injured service members awaited extrication to higher echelons of care¹³. A patient's skin color and temperature were used as a barometer for perfusion. Current algorithms established by The Committee on Tactical Combat Casualty Care and practiced by battle field medics during the initial management of the injured warfighter use a similar approach.³ These guidelines recommend no fluid resuscitation unless inadequate organ perfusion is manifest as evidenced by the quality of the radial pulse or diminished mental status.^{3,14} If there is evidence of shock, a single 500cc bolus of Hextend is given and it may be repeated once.

Given the benefits seen with hypotensive and fluid restricted resuscitation protocols, we hypothesized that delivery of any pre-hospital IVF would be associated with increased survival compared to no pre-hospital IVF in trauma patients.

Methods

Ten Level-1 trauma centers participated in this study. Local Institutional Review Board and US Army Medical Research and Materiel Command Office of Research Protection, Human Research Protections Office approval was obtained for all clinical sites. Prospective data from 1245 trauma patients were collected. These patients were originally enrolled in the Prospective Observational Multi-center Massive Transfusion Study (PROMMTT), a project which examined the timing and amount of in-hospital blood product transfusions and subsequent outcomes¹⁵. Forty-five patients were excluded due to incomplete information. All data were stratified by presence or absence of pre-hospital IVF; 84% (n = 1009) received pre-hospital IVF, and 16% (n = 191) did not.

Patient demographics (gender, age, Injury Severity Score (ISS)), injury mechanisms, pre-hospital IVF volumes, pre-hospital and Emergency Department (ED) vital signs and life-saving interventions (LSI), laboratory values (Basic Metabolic Panel, Hemoglobin, Hematocrit, Platelets, Prothrombin Time (PT), International Normalized Ratio (INR), Partial Thromboplastin Time (PTT), Fibrinogen) and outcomes (morbidity and complications) were collected by direct observation or by record abstraction.^{16,17} The attending physicians classified in-hospital mortality by etiology: head injury, exsanguination, airway compromise, sepsis, multiple organ failure or "other" causes. "Other" causes represented any mechanism which did not meet the aforementioned classifications. The site at which each patient received treatment was assigned a number (1 through 10) and was included with their respective information.

All data were analyzed with the Statistical Package for the Social Sciences (SPSS), Version 19 (IBM, Armonk, New York). During the analysis, the data remained stratified into two groups based upon the presence or absence of pre-hospital IVF administration. Using the Shapiro-Wilk test, all continuous data were tested for normality. Mann-Whitney U tests were used to assess all non-parametric continuous data. Chi-squared tests were used to analyze the nominal data. Intra-group comparisons of on-scene and ED admission variables were made with a Wilcoxon Matched Pairs Signed Ranks test.

Cox regression analyses were employed to assess the influence of pre-hospital IVF on outcome and complications. The other covariates were age, gender, mechanism of injury, ISS, ED Glasgow Coma Scale (GCS) and pre-hospital fluid volume. These covariates have been shown to directly affect outcomes of trauma patients.^{18,19} Finally, Kruskal-Wallis tests were used to determine the influence of site on ISS and pre-hospital IVF volume administered. A significant difference was defined as $p \leq 0.05$.

Results

All continuous variables were initially tested and were found to be non-normal, therefore, where applicable, results are presented as medians and inter-quartile ranges (IQR).

Demographics

There were 1245 patients enrolled in our study. Forty-five were removed due to incomplete pre-hospital fluid data. Four did not have a mechanism of injury listed. There was no difference in gender, age, ISS, hospital length of stay, days of ICU care, or duration of mechanical ventilation between the two groups (Table 1). Blunt trauma occurred more frequently than penetrating trauma, 64.5% (n=771) vs. 35.5% (n=425). Four patients did not have a reported mechanism of injury. Blunt trauma patients were more likely to receive pre-hospital IVF, 86% vs. 81% ($p < 0.001$). There was no difference in mortality associated with the mechanism of injury and the receipt of pre-hospital IVF analyzed utilizing univariate analysis.

Sites

There were ten Level 1 trauma centers in the study (Table 2). The highest number of patients (306) was seen at site 1. The fewest (28) were seen at site 10. More men than women were admitted to the ED at each trauma center. Except for sites 7 and 10, which saw a nearly equal distribution of blunt and penetrating injuries, blunt trauma was more common. Patients at site 8 had the highest median ISS, 34 (IQR 22-43) and the highest mortality, 35%. Conversely site 6 had the lowest median ISS, 17 (IQR: 10-27). Regarding pre-hospital IVF, the median volume of fluid given to the IVF group was 700ml (IQR: 300-1300). Site 8's median, 1500ml (IQR: 900-2500), was the highest and was significantly different than all other trauma centers. Site 7's median, 250ml (IQR: 100-500), was the lowest. The Kruskal-Wallis tests demonstrated that ISS and IVF differed by site ($p < 0.001$).

Vital signs and laboratory work

There was a statistically significant difference in reported on-scene median SBP (100 mmHg vs. 110 mmHg) between the fluid (n=570) and non-fluid (n=99) groups respectively (Table 3). Forty-four percent of the patients (n=531) did not have a reported on-scene SBP. Upon arrival to the ED, a statistically significant difference persisted, 105 mmHg vs. 110 mmHg. The IVF group's 5 mmHg increase after administration of IVF and transport to the ED was not a significant change ($p = 0.20$). There was no difference in other vital signs. ED GCS was significantly lower in the fluid group.

The ED basic metabolic panel (BMP) chloride was higher in the IVF group compared to the non-fluid group, 105 mmol/L (IQR: 103-108) vs. 107 mmol/L (IQR: 104-110, $p < 0.01$) (Table 3). Hemoglobin, hematocrit, platelet count and fibrinogen were lower in the IVF group ($p < 0.01$), while PT, PTT, and INR were higher ($p < 0.05$).

Life-saving interventions

Six LSIs were assessed in the field and twelve in the ED (Table 4). Field intubation was performed more frequently in the IVF group and was the only intervention which demonstrated an inter-group difference, 38% vs. 14% ($p < 0.01$). Upon arrival to the ED, LSIs were performed with equal frequency between the two groups. Massive transfusion (defined as 10 units of RBCs within 24 hours of admission) was the most common ED LSI.

Outcomes

There was no difference in overall unadjusted in-hospital mortality between the two groups, 21% vs. 23% ($p = 0.43$, Table 5). Controlling for age, gender, mechanism of injury, ISS, ED and GCS, a Cox regression demonstrated that pre-hospital IVF were associated with decreased in-hospital mortality, Hazard Ratio (HR): 0.84 (95% Confidence Interval (CI): 0.72-0.98; $p = 0.03$). Mortality was not affected by IVF volume. An inter-quartile IVF volume analysis did not reveal increased mortality with increased fluid administration.

Death from head injuries, a subset of overall mortality, was not significantly different between groups, 9% vs. 8% ($p = 0.65$). In a Cox regression analysis adjusting for the same confounders as previously noted, pre-hospital fluid resuscitation was associated with decreased in-hospital mortality due to head injury, HR: 0.69 (95% CI: 0.54-0.88; $p < 0.01$). As expected, in-hospital mortality due to head injury was associated with a higher AIS, 5 (IQR: 3.5-5), vs. 3 (IQR: 2-4), ($p < 0.001$).

The most common complication was deep venous thrombosis (DVT) but the incidence did not differ between groups (Table 5). ACS was the only complication which differed between the two groups. It was more common in the non-fluid group, 5% vs. 0.7% ($p < 0.01$). There was no difference in fluids given during the first 24 hours between the non-fluid and IVF groups, 14.9L (IQR: 12.6L-39.0L) vs. 18.1L (IQR: 13.9L-43L) respectively, ($p = 0.58$). However patients who developed ACS received more fluid in the first 24 hours of their hospital stay than patients who did not, 17.0L (IQR: 14.1L-35.8L) vs. 11.5L (IQR: 8.1L-17.2L), ($p < 0.01$), therefore development of ACS was unlikely related to pre-hospital fluid resuscitation but rather in-hospital management.

Discussion

We hypothesized that receiving pre-hospital IVF confers a survival benefit in trauma patients. Using a Cox regression analysis, it was shown that pre-hospital IVF were associated with lower in-hospital mortality after trauma. Overall those who received IV fluids experienced decreased in-hospital mortality compared to those who did not. The IVF complications encountered were found to be related to in-hospital management rather than pre-hospital resuscitation.

Our pre-hospital IVF population had a lower on-scene and ED SBP than the non-fluid group. This group received a median pre-hospital fluid volume of 700ml which was less than the 1-2 liters recommended by current PHTLS protocols.³ The volume of fluids given was not adequate to produce a change in blood pressure or alternatively the fluid administration may have prevented the development of hypotension. Additionally, the SBP compared between the two groups differed by 10mmHg when on scene and by 5mmHg

when in the ED, both comparisons were statistically significant but unlikely to be clinically relevant.

Regarding the ED laboratory results, the patients who received pre-hospital IVF demonstrated a significantly higher PT/INR, PTT, and fibrinogen. These changes may constitute the emergence of the coagulopathy of trauma or developing dilutional coagulopathy. The lower hemoglobin and hematocrit in the IVF group is likely a product of the fluids given. Although the median chloride values were different between groups, the difference was 2 mmol/L which is unlikely to be clinically relevant.

Our study reveals that resuscitation with IV fluids is beneficial to trauma patients. There are known complications, i.e. ACS, ARDS, and mortality, associated with over resuscitation. This volume threshold was addressed in a recent retrospective investigation of 370 trauma patients which segregated the population based upon pre-hospital fluid volume.¹¹ They were divided into a standard (greater than 150ml) or restrictive (less than 150ml) fluid resuscitation group. All of the patients underwent damage control surgery. The patients who underwent restrictive resuscitation demonstrated a survival advantage compared to the standard group. Even though both groups received IVF, a volume threshold demarcating improved outcomes was obvious. This threshold was not apparent in our patient population with respect to mortality when we investigated administered fluid volumes by quartile. Our IVF volumes were likely not substantial enough to produce similar results.

Cannon and Beecher advocated for a lower pre-intervention blood pressure reducing the incidence of hemorrhage^{13,20}. The benefits of which were seen in a recent hypotensive resuscitation study targeting mean arterial pressures of 50 mmHg and 65 mmHg¹⁰. Even though the targeted blood pressures were not achieved and there was no significant difference in blood pressure or volume of fluid given between the groups, those maintained at a lower MAP had a significant decrease in postoperative coagulopathy and a reduced risk of postoperative death. Our study also demonstrated that the group with the lower blood pressure, the IVF group, had a higher survival rate.

Finally a study investigating immediate versus delayed fluid resuscitation in penetrating torso trauma also demonstrated improved outcomes within the delayed resuscitation group². There was a significant inter-group difference in the amount of pre-operative fluids given, however there was no difference in the volume given intra-operatively. The time-delay resuscitation resulted in a shorter hospitalization and increased survival to discharge.

The aforementioned studies demonstrate that the traditionally recommended PHTLS volumes and immediate resuscitation practices may not produce optimal results. Additionally, the studies addressed fluid resuscitation and the avoidance of blood pressure elevation potentially resulting in displacement of established clots and recurrent hemorrhage. The lower blood pressures seen in the aforementioned studies were targeted values; blood pressure maintenance was not a criterion for our patient population. The blood pressure seen was lower in the IVF group prior to the initiation of pre-hospital fluids and after arrival to the emergency department. Even though the IVF group's median blood pressure was not identical to previous studies, the less than recommended fluid volume and lack of an increase in blood pressure observed may have played a role in the survival benefit seen.

There were several limitations to our study. This was an analysis of data accumulated over ten geographically distinct trauma centers from a study in which the primary focus was to investigate in-hospital trauma transfusion protocols. Pre-hospital data collection was not the priority of the PROMMTT study and thus the data utilized to perform this analysis may not have been optimal. This analysis also did not account for on-scene SBP due to high levels of

missingness (44%). Because PROMMTT was an observational study and did not impose standardized procedures, diagnostic testing obtained on admission was not uniform and thus data was missing for patients who did not undergo these tests.

We attempted to control for site differences in our Cox regression, but when trauma center was included as an independent predictor in the multivariate model, the model did not converge for many of the outcomes or complications due to small sample numbers. To be able to assess the effect of IVF administration, the site variable was removed from the model. This approach treats the entire population as if they were from one clinical center rather than ten different centers and thus residual confounding by unmeasured clinical site practice differences could be present in our analysis. This approach also eliminated the site bias with regard to fluid administration and number of patients seen at a single institution. Other covariates that were considered clinically relevant were retained in all models. Complications which occurred in less than 1% of the population were not part of the multivariable model due to small numbers of events. Finally, mortality classifications were not independently or centrally adjudicated and the study methodology did not permit assessment of multiple causes of death.

During World War I, Captain W. B. Canon stated “Injection of a fluid that will increase blood pressure has dangers in itself. If the pressure is raised before the surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost.”²⁰ This concept has plagued modern day resuscitation algorithms. Our study demonstrated that administration of pre-hospital IVF conferred a protective advantage and was associated with decreased mortality. Resuscitation protocols which maximize the pre-hospital fluid's benefit while conscientiously avoiding an elevated blood pressure should become standard.

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Table 1
Patient characteristics of 1200 PROMMTT patients by prehospital IVF status

Study population	IVF group (n = 1009)	No IVF group (n = 191)	p
Men (n = 887)	754 (85%)	133 (15%)	0.15
Women (n = 313)	255 (81%)	58 (19%)	
Age	38 (24, 54)	41 (25, 55)	0.59
ISS	25 (16, 34)	25 (16, 35)	0.22
Mechanism of Injury *			
Blunt Trauma (n = 771)	663 (86%)	108 (14%)	0.02
Penetrating Trauma (n = 425)	343 (81%)	82 (19%)	0.02
Mortality			
Blunt Trauma (n = 190)	160 (84%)	30 (16%)	0.25
Penetrating Trauma (n = 67)	52 (78%)	15 (22%)	0.29
Hospitalization			
Length of stay (days)	10 (4, 22)	11.8 (4,23)	0.23
ICU length of stay (days)	4 (1, 14)	4.5 (1, 13)	0.38
Length of mech. ventilation (days)	1 (1, 6.7)	1 (0, 7)	0.95

* 4 patients' mechanism of injury was not reported

Table 2

Characteristics of 1200 PROMMTT patients by clinical site

	Sites									
	1	2	3	4	5	6	7	8	9	10
Demographics										
N	306	134	61	127	121	109	99	121	94	28
Men	223	104	42	95	95	80	75	82	68	23
Women	83	30	19	32	26	29	24	39	26	5
Injury										
Blunt	213	61	40	98	92	66	50	84	56	17
Penetrating	93	73	21	29	29	43	49	37	38	11
Unknown	0	1	0	0	0	0	0	0	3	5
Death	68	23	14	22	18	19	23	42	24	5
Death %	22.2	17.2	23.3	17.2	13.5	17.3	22.1	34.7	25.0	17.9
ISS										
Score	25 (16-34)	25 (16-34)	29.5 (18.2-42)	22 (16-34)	24 (13-35.5)	17 (10-27)	22 (16-35)	34 (22-43)	22 (10.2-34)	20.5 (9-35.5)
Significant to other sites *	6.8	6.8	6	6.8	8	1-4,8	8	1,2,4,7,9	8	-
Fluids										
IVF given (ml)	775 (350-1287)	500 (250-1000)	450 (200-775)	500 (375-1000)	800 (300-1700)	800 (425-1200)	250 (100-500)	1500 (900-2500)	750 (362-1500)	1000 (500-1000)
Significant to other sites *	2,7,8	1,5,8	8	7,8	2,7,8	7,8	1,4-6,8-10	1-7,9,10	7,8	7,8

* Significant differences 0.001

Table 3
EMS and admission vital signs and laboratory values from 1200 PROMMTT patients by pre-hospital IVF fluid status

	IVF group (n = 1009)	No IVF group (n = 191)	p
On-scene			
Heart Rate (bpm)	107 (88.7, 120)	102 (88, 120)	0.40
Systolic blood pressure (mmHg)	100 (84, 124)	110 (90, 130)	0.04
Respiratory rate (Respirations/min)	20 (16, 24)	20 (16, 22)	0.27
Emergency Department			
Temperature (°F)	97 (96.0, 97.9)	97.1 (95.9, 97.9)	0.74
Heart Rate (bpm)	105 (86, 124)	107 (88, 122)	0.84
Systolic blood pressure (mmHg)	105 (85, 126)	110 (88, 138)	0.05
Diastolic blood pressure (mmHg)	67 (53, 82)	70 (52, 90)	0.08
Respiratory rate (Respirations/min)	20 (18, 25)	20 (18, 27)	0.96
SpO2 (%)	98 (73, 100)	96.4 (83, 100)	0.94
GCS	13 (3, 15)	15 (6, 15)	< 0.01
GCS (Eye)	3 (1, 4)	4 (1, 4)	< 0.01
GCS (Verbal)	4 (1, 5)	5 (1, 5)	< 0.01
GCS (Motor)	6 (1, 6)	6 (3, 6)	< 0.01
Basic Metabolic Panel			
Sodium (mEq/L)	140.0 (138.0, 142.0)	140.0 (138.0, 142.0)	0.91
Potassium (mEq/L)	3.6 (3.3, 4.1)	3.7 (3.3, 4.0)	0.76
Chloride (mmol/L)	107.0 (104.0, 110.0)	105.0 (103, 108.0)	< 0.01
Bicarbonate	NR	NR	NR
BUN (mg/dl)	14.0 (10.0, 17.0)	15.0 (10.0, 18.0)	0.14
Cr (mg/dl)	1.1 (0.9, 1.3)	1.12 (0.93, 1.4)	0.34
Glucose (mg/dl)	167.0 (140.0, 217.0)	169 (130, 210)	0.25
Blood Count			
Hemoglobin (gm/dl)	11.6 (10.0, 13.2)	12.5 (10.8, 13.8)	< 0.01
Hematocrit (%)	34.3 (30.0, 38.8)	37 (32.0, 40.2)	< 0.01
Platelets (K/dl)	223 (178.0, 273.5)	238 (192.0, 297.5)	< 0.01
Coagulation			
Fibrinogen (mg/dl)	211.0 (152.0, 287.0)	257.5 (190.5, 377.7)	< 0.01
PT (sec.)	15.2 (13.7, 17.5)	14.4 (13.3, 15.6)	< 0.01
INR	1.2 (1.1, 1.5)	1.14 (1.08, 1.28)	< 0.01
PTT (sec.)	28.0 (24.1, 33.2)	27 (23, 31.6)	0.03

Significant difference: p = 0.05

NR - Not Recorded

Table 4
Life saving intervention data from 1200 PROMMTT patients by pre-hospital IVF status

On-scene	IVF group(n = 1009)	No IVF group(n = 191)	p
Life-saving intervention	418 (41%)	38 (20%)	< 0.01
CPR	18 (2%)	5 (3%)	0.53
Intubation	385 (38%)	27 (14%)	< 0.01
Cardioversion	1 (0.1%)	1 (0.5%)	0.30
Needle thoracocentesis	51 (5%)	8 (4%)	0.64
Cricothyroidotomy	0 (0%)	0 (0%)	0.41
Tourniquet	2 (0.2%)	1 (0.5%)	0.39
Emergency Department			
Life-saving intervention	489 (48%)	103 (54%)	0.35
CPR	48 (5%)	5 (3%)	0.38
Intubation *	13 (2%)	1 (0.6%)	0.2
Cardioversion	6 (0.6%)	0 (0%)	0.51
Needle thoracocentesis	8 (0.8%)	4 (2%)	0.23
Cricothyroidotomy	5 (0.5%)	0 (0%)	0.57
Tourniquet	33 (3%)	9 (5%)	0.56
Chest thoracocentesis	280 (28%)	49 (26%)	0.76
Pericardiocentesis	2 (0.2%)	0 (0%)	0.75
Thoracotomy	19 (2%)	4 (2%)	0.89
Traction splint	48 (5%)	8 (4%)	0.86
ICP/Ventriculostomy	8 (1%)	1 (0.5%)	0.84
Massive transfusion	344 (34%)	62 (32%)	0.31

Significant difference: p = 0.05

* Among patients not intubated on-scene, IVF group (n = 614), and no IVF group (n = 161)

Table 5
Mortality and complications data from 1200 PROMMTT patients by pre-hospital IVF status

Mortality	IVF groupn = 1009	No IVF groupn = 191	p	Cox Regression	
				HR (95% CI)	p
Overall	212 (21%)	45 (23%)	0.43	0.84 (0.72, 0.98)	0.03
Exsanguination	82 (8%)	14 (7%)	0.71	1.08 (0.86, 1.33)	0.52
Head injury	95 (9%)	16 (8%)	0.65	0.69 (0.54, 0.88)	< 0.01
Airway	29 (3%)	7 (4%)	0.56	0.64 (0.40, 1.0)	0.07
Sepsis	7 (0.7%)	1 (0.5%)	0.79	*	*
Multi-organ failure	23 (2%)	6 (3%)	0.48	0.64 (0.36, 1.14)	0.13
Cardio-vascular	45 (4%)	6 (3%)	0.41	0.99 (0.71, 1.37)	0.94
Other	24 (2%)	13 (7%)	< 0.01	0.75 (0.48, 1.19)	0.22
Complications					
Cardiac Arrest	9 (1%)	2 (2%)	0.83	0.37 (0.12, 1.18)	0.09
Pulmonary Embolism	24 (3%)	5 (4%)	0.83	1.25 (0.87, 1.80)	0.24
Myocardial infarction	2 (0.3%)	1 (0.8%)	0.40	*	*
Deep venous thrombosis	43 (6%)	13 (10%)	0.13	1.14 (0.84, 1.55)	0.39
Cerebrovascular event	11 (2%)	2 (2%)	0.97	*	*
Septic shock	19 (3%)	3 (2%)	0.77	1.00 (0.58, 1.73)	0.99
Vasopressor dependent shock	11 (1%)	1 (0.8%)	0.48	*	*
Abdominal compartment syndrome	5 (0.7%)	6 (5%)	< 0.01	0.49 (0.17, 1.43)	0.19
Renal failure	17 (3%)	3 (2%)	0.92	1.02 (0.55, 1.91)	0.95
Acute lung injury	0 (0%)	0 (0%)	**	**	**
Acute respiratory distress syndrome	2 (0.2%)	0 (0%)	0.54	*	*
Multiple organ failure	13 (1%)	2 (1%)	0.78	0.96 (0.52, 1.77)	0.88

Significant difference: p 0.05

* Model did not converge, too few were events reported

** No cases reported